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The impact of dietary consistency on structural craniofacial components: Temporomandibular joint/condyle, condylar cartilage, alveolar bone and periodontal ligament. A systematic review and meta-analysis in experimental in vivo research

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Abstract: OBJECTIVE The aim of this systematic review was to provide a comprehensive synthesis of available evidence evaluating the effect of dietary loading on temporomandibular joint/condyle, condylar cartilage, alveolar bone of the mandible and the periodontal ligament in healthy mice and rats. DESIGN Medline via PubMed, EMBASE and Open Grey databases were searched for published and unpublished literature. Search terms included ”mandiblular condyle”, ”alveolar bone”, ”temporomandibular joint”, ”condylar cartilage”, ”periodontal ligament”, ”rat”, ”mice”. After data extraction, risk of bias (SYRCLE) and reporting quality (ARRIVE) were assessed. Random effects meta-analyses were performed for the outcomes of interest where applicable. RESULTS A total of 33 relevant articles were considered in the systematic review, while only 6 studies were included in the quantitative synthesis. Risk of Bias in all studies was judged to be unclear to high overall, while reporting quality was suboptimal. Comparing soft to hard diet animals, significantly reduced anteroposterior condylar length (4 studies, weighted mean difference: -0.40 mm; 95% CI: -0.47, -0.32; $p < 0.001$) and width (4 studies, weighted mean difference: -0.043 mm; 95% CI: -0.51, -0.36; $p < 0.001$) were found in rats. Decreased anteroposterior condylar dimensions were detected for mice as well (2 studies, weighted mean difference: -0.049; 95% CI: -0.56, -0.43; $p < 0.001$). CONCLUSIONS Overall, there was strong evidence to suggest a significant effect of soft diet on reduced condylar dimensions in rodents; however, there is need for further high quality experimental studies to inform current knowledge on condylar cartilage, alveolar bone and periodontal ligament related outcomes.

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The impact of dietary consistency on structural craniofacial components: temporomandibular joint/condyle, condylar cartilage, alveolar bone and periodontal ligament. A systematic review and meta-analysis in experimental in vivo research.

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Running Title: Dietary consistency and craniofacial components

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The impact of dietary consistency on structural craniofacial components: temporomandibular joint/condyle, condylar cartilage, alveolar bone and periodontal ligament. A systematic review and meta-analysis in experimental in vivo research.

Structured Abstract

Objective

The aim of this systematic review was to provide a comprehensive synthesis of available evidence evaluating the effect of dietary loading on temporomandibular joint/condyle, condylar cartilage, alveolar bone of the mandible and the periodontal ligament in healthy mice and rats.

Design

Medline via PubMed, EMBASE and Open Grey databases were searched for published and unpublished literature. Search terms included ”mandiblular condyle”, “alveolar bone”, “temporomandibular joint”, “condylar cartilage”, “periodontal ligament”, “rat”, “mice”. After data extraction, risk of bias (SYRCLE) and reporting quality (ARRIVE) were assessed. Random effects meta-analyses were performed for the outcomes of interest where applicable.

Results

A total of 33 relevant articles were considered in the systematic review, while only 6 studies were included in the quantitative synthesis. Risk of Bias in all studies was judged to be unclear to high overall, while reporting quality was suboptimal. Comparing soft to hard diet animals, significantly reduced anteroposterior condylar length (4 studies, weighted mean difference: -0.40mm; 95%CI: -0.47, -0.32; p<0.001) and width (4 studies, weighted mean difference: -.043mm; 95%CI: -0.51, -0.36; p<0.001) were found in rats. Decreased anteroposterior condylar dimensions were detected for mice as well (2 studies, weighted mean difference: -.049; 95%CI: -0.56, -0.43; p<0.001).

Conclusions

Overall, there was strong evidence to suggest a significant effect of soft diet on reduced condylar dimensions in rodents; however, there is need for further high quality experimental studies to inform current knowledge on condylar cartilage, alveolar bone and periodontal ligament related outcomes.

Keywords: hard diet, soft diet, condyle, alveolar bone, periodontal ligament, craniofacial

1. Introduction

During the course of human evolution, adaptations in human dental apparatus and craniofacial complex have taken place. Maxillary and mandibular bones have decreased in size, giving rise in tooth to alveolar bone discrepancies (Hanihara, Inoue, Ito, & Kamegai, 1981; Shiono, Ito, Inuzuka, & Hanihara, 1982) and increasing prevalence of malocclusions (Kelly & Harvey, 1977). According to anthropologic data, this is a relatively recent phenomenon whereas a much lower incidence of malocclusions has been reported for "primitive" populations (Beyron, 1964; Hunt, 1961; Liu, 1977; Lombardi & Bailit, 1972; Price, 1936; Wood, 1971). Notwithstanding, the form to function relationship of the jaws is genetically controlled and this has been demonstrated in inherited occlusal patterns pertaining within families (Kraus, Wise, & Frei, 1959; Lundström, 1948) or in whole ethnic groups (Björk, 1947; Cotton, Takano, & Wong, 1951; Craven, 1958); however not all phenotypic changes are due to the underlying genetic information. In early 1900s, the German anatomist and surgeon Wolff discovered that the internal architecture of femoral bone responds to external mechanical stress (Wolff, 2010). This constant adaptation of the trabecular bone can also be observed in the condylar process of the mandible and is ultimately based on variations in the level of activity of masticatory muscles.

In industrialized communities, life circumstances have changed dramatically with a subsequent impact on nutrition consistency. The dietary pattern has switched to "modern" processed diet which is softer and which goes along with a more limited use of the masticatory apparatus (Corruccini & Lee, 1984; Waugh, 1937). The masticatory system itself is a complex neuro-musculoskeletal system constituting from different parts, containing the horseshoe-shaped lower jaw body (corpus mandibulae) that supports the alveolar bone process which houses the teeth and their surrounding periodontal ligament. The lower jaw as a whole is connected with the masticatory muscles and the temporomandibular joint (TMJ) to the rest of the skull. The TMJ has always been the center of research interest as it consists of the condylar process and cartilage which is a highly adaptive and respondent to mechanical stress tissue (Eames & Schneider, 2008). As the force exerted on the TMJ is assumed to be greater during the mastication of hard food in contrast to softer diets (Boyd, Gibbs, Mahan, Richmond, & Laskin, 1990), a change in food consistency would inevitably pose an effect on the structures of the craniofacial system.

Due to ethical reasons, experimental evidence in human is very difficult to prove; however, a number of parameters have been examined in laboratory animal models. Rodents and in particular mice and rats have been used for this purpose since they are easy to handle, inexpensive to maintain and show a close genetic background to human, making them a convenient animal model for use. Animal studies in general have shown a direct causal relationship between reduced masticatory muscle function and modified dietary consistency. Soft diet has been linked with alterations in the muscle fiber composition, decreased fiber diameter, reduced total muscle weight and reduced masticatory muscle strength, which in turn has a subsequent effect on the craniofacial complex especially in growing animals (Beecher & Corruccini, 1981b; Kiliaridis, Engström, & Thilander, 1988; Kiliaridis & Shyu, 1988; Moore, 1965).

Although extensive animal studies have been published addressing the impact of dietary consistency upon both the hard and soft tissues, no systematic review has been performed in an attempt to place individual study conclusions into the appropriate context.

Therefore, the objective of this systematic review was to provide a comprehensive synthesis evaluating the effect of dietary loading on temporomandibular joint/condyle, condylar cartilage, alveolar bone of the mandible and the periodontal ligament in healthy mice or rats.

2. Material and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009) were followed for reporting of this systematic review.

2.1 Eligibility Criteria

The following inclusion criteria were applied:

- Study design: Randomized or non-randomized experimental studies involving rodents were considered.
- Population/ Animal: Any laboratory strain of rat or mice at any age.
- Interventions: Soft diet administration for a given time period
- Comparators: Hard/Normal diet administration for a similar time period.
- Outcome measures: Effect of different type of dietary loading (ie soft/hard) on: 1. Temporomandibular joint/condylar process , 2. Condylar Cartilage , 3. Alveolar bone of the mandible and 4. Periodontal ligament.

Exclusion Criteria:

- In vitro studies
- Animal studies without a comparison group
- Animal studies involving diet switching (from hard to soft and/or vice versa)
- Not healthy animal populations (ie, diabetic, ovariectomized etc)
- Animals being subject to other simultaneous interventions (ie incisor trimming, bite-blocks etc)
- Studies pertaining to molecular, genetic, biochemical outcomes.

2.2 Search Strategy

Electronic search within the following databases was undertaken in January 14, 2017, while no language restrictions were applied: Medline via Pubmed and EMBASE were searched.

Moreover, unpublished literature was searched in Open Grey using the terms «diet» AND «rat OR mice». Hand searching of the reference lists of the retrieved full text articles was also conducted. Authors of original studies were contacted for data clarification if needed. Full search strategy implemented in Medline via Pubmed is presented in Appendix 1.

2.3 Data Extraction

Data extraction was performed on standardised piloted forms by one independently working reviewer (RS) and confirmed by a second (DK), both of whom were not blinded to author identity and study origin. Titles and abstracts were examined first, while at a second stage full text screening of the potential for inclusion articles was employed. Information was obtained from each included study on study design, population (type of animal), interventions, comparators and outcomes. In addition, information on duration of experiment and age of animals at the beginning of the active period of study was recorded. Any disagreements or ambiguity were resolved after consultation with a third author (TE).

2.4 Reporting quality

Reporting quality of the studies was assessed based on adherence to ARRIVE guidelines for reporting of animal studies (Kilkenny, Browne, Cuthill, Emerson, & Altman, 2010). According to completeness of reporting, the reporting quality was judged as “clearly inadequate”, “possibly inadequate” and “clearly adequate”. A grading system of 20 items contributed to the overall judgement of reporting quality (Table 1).

2.5 Risk of bias within studies

Risk of bias (RoB) in individual studies was assessed in line with the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) RoB tool for animal studies (Hooijmans et al., 2014). In particular, the following ten domains were considered: 1.

Sequence generation, 2. Baseline characteristics, 3. Allocation concealment, 4. Random housing, 5. Blinding of researchers, 6. Random outcome assessment, 7. Blinding of outcome assessors, 8. Incomplete outcome data, 9. Selective outcome reporting, 10. Other sources of bias.

An overall assessment of the risk of bias was made for each included study (high, unclear, low). Studies with at least 1 item designated to be at high risk of bias were regarded as having an overall high risk of bias. Reports with unclear risk of bias for one or more key domains were considered to be at unclear risk of bias and studies with low risk of bias in all domains were rated as low risk of bias.

2.6 Summary Measures and Data Synthesis

Clinical homogeneity of included studies was assessed through the examination of individual trial settings, eligibility criteria, interventions, experimental conditions, animal age and observation time. Statistical heterogeneity was examined through visual inspection of the confidence intervals (CIs) for the estimated treatment effects on forest plots. Also, a chi-square test was applied to assess heterogeneity; a p-value below the level of 10% ($p<0.1$) was considered indicative of significant heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). I^2 test for homogeneity was also undertaken to quantify the extent of heterogeneity.

Random effects meta-analyses were conducted as they were considered more appropriate to better approximate expected variations in studies' settings. Treatment effects were calculated through pooled weighted mean differences (WMD) in all outcome related parameters with associated 95% Confidence Intervals (95% CIs) and Prediction Intervals where applicable (at least 3 trials needed).

2.7 Risk of bias across studies

If more than 10 studies were included in meta-analysis, publication bias was to be explored through standard funnel plots.

2.8 Additional Analyses

Sensitivity analyses were pre-specified to explore and isolate the effect of studies with low risk of bias on the overall treatment effect if both low and higher risk of bias studies were included.

3. Results

3.1 Search Details

The flow diagram of the study selection is presented in Figure 1. The electronic search identified 995 articles, while records of 20 articles were identified after hand searching of the included for full-text evaluation studies. After the review of the titles, the abstracts and the full text manuscripts 33 studies were considered eligible for inclusion in the review, while 6 were eligible for quantitative evaluation.

3.2 Study design and location

In 15 studies (Abed, Buschang, Taylor, & Hinton, 2007; Bresin, Kiliaridis, & Strid, 1999; Endo, Mizutani, Yasue, Senga, & Ueda, 1998; Enomoto et al., 2014; Enomoto et al., 2010; Guerreiro et al., 2013; Hichijo et al., 2014; Hinton & Carlson, 1986; Ikeda, Yonemitsu, Takei, Shibata, & Ono, 2014; Kingsmill, Boyde, Davis, Howell, & Rawlinson, 2010; Maki, Nishioka, Shioiri, Takahashi, & Kimura, 2002; McFadden, McFadden, & Precious, 1986; Shimizu et al., 2013; Tanaka et al., 2007; Vaid, Pradhan, & Chakrabarti, 2002), the animals were randomly allocated to either hard or soft diet feeding group, although no details of the randomization procedure were reported. In the rest (n= 18) of the studies (Barber, Green, & Cox, 1963; Beecher & Corruccini, 1981a; Bouvier, 1988; Bouvier & Hylander, 1984; Bouvier & Zimny, 1987; Bresin, Johansson, & Kiliaridis, 1994;Bresin, Kiliaridis, & Strid, 1999; Ito, Mitani, & Kim, 1988; Kiliaridis, Bresin, Holm, & Strid, 1996; Mavropoulos, Odman, Ammann, & Kiliaridis, 2010; Odman, Mavropoulos, & Kiliaridis, 2008; Orajarvi, 2015; Orajarvi et al., 2011; Orajarvi et al., 2012; Stahl & Dreizen, 1964; Tiilikainen, Raustia, & Pirttiniemi, 2011; Watt & Williams, 1951; Yamada & Kimmel, 1991) no obvious randomization was done or allocation was implemented by convenience. The country of origin (according to corresponding author affiliation) of the studies were Japan (Endo et al., 1998; Enomoto et al., 2014; Enomoto et al., 2010; Hichijo et al., 2014; Ikeda et al., 2014; Ito et al., 1988; Maki et al., 2002; Shimizu et al., 2013; Tanaka et al., 2007; Yamada & Kimmel, 1991), United States (Abed et al., 2007; Barber et al., 1963; Beecher & Corruccini, 1981a; Bouvier, 1988; Bouvier & Zimny, 1987; Hinton & Carlson, 1986; Stahl & Dreizen, 1964), Finland (Orajarvi, 2015; Orajarvi et al., 2011; Orajarvi et al., 2012; Tiilikainen et al., 2011), Sweden (Bresin, Johansson, & Kiliaridis, 1994; Bresin, Kiliaridis, & Strid, 1999; Kiliaridis et al., 1996; Odman et al., 2008), Canada (McFadden et al., 1986; Watt & Williams, 1951), Switzerland (Kiliaridis, Thilander, Kjellberg, Topouzelis, & Zafiriadis, 1999; Mavropoulos et al., 2010), Brazil (Guerreiro et al., 2013), India (Vaid et al., 2002), Puerto Rico (Bouvier & Hylander, 1984) and United Kingdom (Kingsmill et al., 2010). In the subgroup of studies dealing with temporomandibular joint/condyle of rats (Barber et al., 1963; Beecher & Corruccini, 1981a; Bouvier, 1988; Bouvier & Hylander, 1984; Bouvier & Zimny, 1987; Bresin, Kiliaridis, & Strid, 1999; Endo et al., 1998; Guerreiro et al., 2013; Hinton & Carlson, 1986; Ikeda et al., 2014; Kiliaridis et al., 1996; Kiliaridis et al., 1999; Maki et al., 2002; McFadden et al., 1986; Odman et al., 2008; Tanaka et al., 2007; Vaid et al., 2002; Watt & Williams, 1951; Yamada & Kimmel, 1991) the sample size ranged from 3 to 30 for both the hard and the soft diet animals The sample size for rat condylar cartilage (Bouvier, 1988; Bouvier & Hylander, 1984; Endo et al., 1998; Hichijo et al., 2014; Hinton & Carlson, 1986; Ikeda et al., 2014; Kiliaridis et al., 1999; Orajarvi, 2015; Orajarvi et al., 2011; Orajarvi et al., 2012; Tiilikainen et al., 2011; Vaid et al., 2002; Yamada & Kimmel, 1991) ranged from 3 to 16, while for the mandibular alveolar bone (Abed et al., 2007; Bresin, Kiliaridis, & Strid, 1999; Kiliaridis et al., 1996; Kingsmill et al., 2010; Mavropoulos et al., 2010; Odman et al., 2008; Shimizu et al., 2013; Tanaka et al., 2007; Watt & Williams, 1951; Yamada & Kimmel, 1991), six to 30 animals were recruited. As for the rat periodontal ligament outcome (Bresin, Kiliaridis, & Strid, 1999; Stahl & Dreizen, 1964), thirteen to fourteen animals were used.

In the subgroup of the mouse temporomandibular joint/condyle (Enomoto et al., 2010; Ito et al., 1988) the sample size ranged from 5 to 20. One study with results pertaining to mouse condylar cartilage was found (Enomoto et al., 2014), consisting of 5 animals in each group. There were no results of interest regarding either the mandibular alveolar bone or the periodontal ligament.

3.3 Animal Population

A total number of 33 studies were included in the review. Thirty studies using rat populations with a total number of 833 animals were considered (250 females and 583 males). Male rats were used in 18 studies (Abed et al., 2007; Barber et al., 1963; Bouvier & Hylander, 1984; Bresin, Johansson, & Kiliaridis, 1994; Bresin, Kiliaridis, & Strid, 1999; Endo et al., 1998; Guerreiro et al., 2013; Hichijo et al., 2014; Hinton & Carlson, 1986; Ikeda et al., 2014; Kiliaridis et al., 1996; Kiliaridis et al., 1999; Maki et al., 2002; Mavropoulos et al., 2010; Odman et al., 2008; Shimizu et al., 2013; Stahl & Dreizen, 1964; Tanaka et al., 2007), female in 6 (Kingsmill et al., 2010; Orajarvi, 2015; Orajarvi et al., 2011; Orajarvi et al., 2012; Tiilikainen et al., 2011; Yamada & Kimmel, 1991) while 6 studies used both sexes (Beecher & Corruccini, 1981a; Bouvier, 1988; Bouvier & Zimny, 1987; McFadden et al., 1986; Vaid et al., 2002; Watt & Williams, 1951). The age at the beginning of the intervention ranged from 2 weeks to 4 months for the rat species, while most of the studies used 3 week old animals (63,3%) (Table 2). In addition, three studies dealing with mice (Enomoto et al., 2014; Enomoto et al., 2010; Ito et al., 1988), consisting of a total number of 240 animals (all males) were considered. The starting age for these species ranged from 2 to 3 weeks (Table 3).

3.4 Interventions and observation period

Rats

The observation period for the subgroups of separate outcomes ranged as follows: for the temporomandibular joint/condyle from 26 days to 27 weeks, for the condylar cartilage from 7 days to 17 weeks, for the mandibular alveolar bone from 4 weeks to 27 weeks and for the molar periodontal ligament from 4 weeks up to 66 weeks (Table 2).

Mice

The observation period regarding temporomandibular joint/condyle ranged from 1 week to 18 weeks while for the condylar cartilage from 1 week to 4 weeks respectively. There were no results for the mouse mandibular alveolar bone or the molar periodontal ligament (Table 3).

3.5 Outcomes

The four parameters of interest were evaluated for rats and mice independently and subdivided in different subgroups.

Rats (Table 2)

1. Temporomandibular joint/condylar process:
    - X- ray findings
    - Histologic/histomorphometric findings
    - Condyle length measurements (either anteroposterior length or length of the condyle process perpendicular to a tangent to the notches)
    - Condyle width measurement

- Area of condylar process measurement

2. Condylar Cartilage:
    - Thickness of condylar cartilage (histologic zones)
    - Condylar cartilage depth
3. Alveolar bone of the mandible:
    - X- ray findings
    - Height of molar alveolar bone
    - Width of molar alveolar bone
4. Periodontal ligament:
    - Width of periodontal space

Mice (Table 3)

1. Temporomandibular joint/condylar process:
    - Condyle length measurement
    - Condyle width measurement
2. Condylar Cartilage in general

3.6 Reporting Quality of Included Studies

According to the ARRIVE guidelines (Table 1), information on title was adequate in general although some studies did not define species or used a rather general title (Figure 2). The abstract was adequate as well, with the exception of some older studies (Barber et al., 1963; Beecher & Corruccini, 1981a; Stahl & Dreizen, 1964; Watt & Williams, 1951), where no obvious abstract was available. All but one (Barber et al., 1963) study showed a sufficient background and an adequate description of the study objectives. Only a limited number of studies (Guerreiro et al., 2013; Ikeda et al., 2014; Shimizu et al., 2013) showed complete data regarding ethical statement, some did not report a relevant approval, while more than half reported no information. In general there was an overall moderate reporting quality (ie rated as possibly inadequate) regarding study design and no study reported a clear randomization process. A few studies (18.2%) reported blinding when assessing the results while some provided details of the experimental unit. Overall information regarding experimental procedures was adequate. Regarding the experimental animals, available information was adequate with few exceptions (Beecher & Corruccini, 1981a; Orajarvi, 2015; Orajarvi et al., 2011; Orajarvi et al., 2012; Yamada & Kimmel, 1991) whereas information regarding housing and husbandry was not clearly reported. No study provided information on sample size calculation while in a few the number of animals in each experimental group was unclear (Beecher & Corruccini, 1981a; Bouvier & Zimny, 1987; Endo et al., 1998; Hinton & Carlson, 1986; Ito et al., 1988). All but one study (Barber et al., 1963) reported a detailed outcome evaluation procedure, presented information on statistical analysis (with exception of (Hinton & Carlson, 1986; Ito et al., 1988; Stahl & Dreizen, 1964) and provided baseline data regarding weight prior to testing. Very few studies reported on missing data in each group under evaluation, presented their results with a measure of precision or dealt with information on possible adverse effects. None of the studies referred to the “3 R`s” principle (replacement, refinement and reduction) for experimental animals (Kilkenny et al. 2010), whereas most considered relevance to human biology in the discussion. Funding statement was clearly inadequate or clearly adequate on equal parts (Figure 2).

3.7 Risk of Bias of Included Studies

In 15 studies (45.5%) the animals were “randomly” allocated to different feeding protocols, although no details of the randomization process or allocation concealment were reported (see Figures 3 and 4). Baseline characteristics were almost clearly described. Blinding of the caregivers was rated as unclear as although it was most probably difficult to be implemented given the nature of the intervention, the effect of absence of blinding cannot be disregarded. There were no details regarding the random selection of the animals for outcome assessment. Six studies (18.2%) reported blinding of the outcome assessor to minimize “detection bias.” In the majority of studies it was not clear whether all animals were included in the analyses. Only 5 (15.2%) reported the analyzed number of animals or provided reasoning for missing data. Almost 60 percent of the studies were free from selective outcome reporting providing adequate addressing of the pre-defined outcomes, while 12 studies (36.4%) achieved an unclear rating. Lastly, missing information regarding animal weight at the initiation of the experiments was rated high risk of bias, as this was considered a significant factor contributing to analysis errors since linear dimensions are increased in heavier animals. Overall, eleven studies were identified with missing weight data. An unclear distribution of male and female animals between the intervention groups was classified as another potential source of bias due to sexual dimorphism and was detected in two studies (Beecher & Corruccini, 1981a; Vaid et al., 2002) (Figure 3, Figure 4).

3.8 Effects of interventions, meta-analyses and additional analyses

In the light of the available data, only three syntheses were possible for either rats or mice populations, all pertaining to alterations in condylar dimensions following soft and hard diet.

According the results of random effects meta-analysis regarding anteroposterior condylar length in rat populations, there was strong evidence of significantly reduced length for rats receiving soft diet as compared to those receiving hard (4 studies, weighted mean difference: -0.40mm; 95%CI: -0.47, -0.32; p<0.001; I^2=0.0%, p=0.74; Figure 5). A similar finding was detected when condylar width dimensions were examined (4 studies, weighted mean difference: -.043mm; 95%CI: -0.51, -0.36; p<0.001; I^2=46.7%, p=0.13; Figure 6).

In mice populations, there was strong evidence in favour of significantly smaller condylar length in soft diet groups (2 studies, weighted mean difference: -.049; 95%CI: -0.56, -0.43; $p<0.001$; $I^2=0.0\%$, $p=0.87$; Figure 7).

3.9 Risk of Bias across studies

Exploring for publication bias either statistically or graphically was not undertaken as no more than 4 studies were included in any individual synthesis.

3.10 Summary of main results

Rats (Table 2)

Temporomandibular joint/condylar process

- X- ray findings:

Six studies (Bresin, Kiliaridis, & Strid, 1999; Ikeda et al., 2014; Maki et al., 2002; Tanaka et al., 2007; Watt & Williams, 1951) assessed temporomandibular joint/condylar process on x-rays with five heterogeneous measurement techniques. Initial animal age ranged from three to 4 weeks and observation period from four to 16 weeks. In general, bone showed increased mass/density and higher degree of mineralization in animals fed with hard diet

- Histologic/histomorphometric findings:

Histologic/histomorphometric investigation of the temporomandibular joint/condylar process process took place in four studies (Bouvier, 1988; Bouvier & Hylander, 1984; Hinton & Carlson, 1986; Yamada & Kimmel, 1991). Age at the beginning ranged from 3 weeks to 4 months and observational period lasted from 26 days to 12 weeks. Overall reduced quantity/volume of subchondral bone due to reduced density and size of trabeculae was recorded in soft diet rats.

- Condyle process length, width and area measurement:

Condyle process length measurements were performed in 11 studies (Barber et al., 1963; Beecher & Corruccini, 1981a; Bouvier, 1988; Bouvier & Hylander, 1984; Bouvier & Zimny, 1987; Endo et al., 1998; Guerreiro et al., 2013; Kiliaridis et al., 1999; McFadden et al., 1986; Odman et al., 2008; Vaid et al., 2002), while condylar process width was measured in 6 studies (Bouvier, 1988; Bouvier & Hylander, 1984; Bouvier & Zimny, 1987; Endo et al., 1998; Kiliaridis et al., 1999; Vaid et al., 2002) and condylar process area in two (Barber et al., 1963; Odman et al., 2008). Age at the beginning of the intervention ranged from 2 weeks to 4 months for animals measuring length and width and from 3 to 27 weeks for area measurement respectively. After a period of 4 to 27 weeks using differential diet consumption, increased condylar dimensions were observed in animals fed with hard diet.

Condylar Cartilage

A total number of 13 studies (Bouvier, 1988; Bouvier & Hylander, 1984; Endo et al., 1998; Hichijo et al., 2014; Hinton & Carlson, 1986; Ikeda et al., 2014; Kiliaridis et al., 1999; Orajarvi, 2015; Orajarvi et al., 2011; Orajarvi et al., 2012; Tiilikainen et al., 2011; Vaid et al., 2002; Yamada & Kimmel, 1991) assessed condylar cartilage on histologic sections in all three planes of space. Initial age was three weeks for most studies but ranged from two weeks up to 4 months while the range for the observational period was 2 to 17 weeks. All cartilage zones (articular, proliferative, chondroblastic and hypertrophic) were found to be affected by alterations in diet, with soft diet animals presenting thinner cartilage layers in general. In addition, hard diet animals showed a further increase in the maximum depth of the condylar cartilage when dry condyles were assessed (Bouvier & Hylander, 1984; Vaid et al., 2002).

Molar alveolar bone of the mandible

- X- ray findings:

Six studies (Bresin, Kiliaridis, & Strid, 1999; Kiliaridis et al., 1996; Kingsmill et al., 2010; Mavropoulos et al., 2010; Shimizu et al., 2013; Tanaka et al., 2007) analyzed molar alveolar bone of the mandible - most in the region of the first molar tooth, on x-rays with heterogeneous measurement techniques. Bone sections were examined after an experimental period ranging from 4 to 27 weeks. Bone mass/density and common micro-CT parameters such as ratio bone volume/trabecular volume, trabecular thickness, trabecular number, trabecular spacing width, trabecular volume and connectivity density were found to increase in hard diet animals (Mavropoulos et al., 2010; Shimizu et al., 2013), while other micro – CT parameters such as marrow space, trabecular spacing and bone surface/bone volume ratio decreased (Odman et al., 2008; Shimizu et al., 2013).

- Height and width of molar alveolar bone:

The use of three heterogeneous investigation methods (micro-CT, lateral photographs of dry hemimandibles and lateral cephalograms) for measuring height (Bresin, Johansson, & Kiliaridis, 1994; Mavropoulos et al., 2010; Odman et al., 2008) as well as three methods for measuring width (micro- CT, dry mandible and contact micro-radiograms) (Bresin, Johansson, & Kiliaridis, 1994 ; Mavropoulos et al., 2010; Watt & Williams, 1951) of alveolar bone in the first molar region, revealed an overall increase in both dimensions in hard diet animals (initial age: 3-29 days; observation period: 4-27 weeks).

Molar periodontal ligament

- Width of periodontal space:

Two studies (Bresin, Johansson, & Kiliaridis, 1994; Stahl & Dreizen, 1964) with quite similar initial age (4 to 5 weeks) reported increased periodontal space on histological sections in either mesio- distal or in bucco- lingual direction in hard diet animals.

Mice (Table 3)

Three studies (Enomoto et al., 2014; Enomoto et al., 2010; Ito et al., 1988) assessed the temporomandibular joint/condylar process through measuring the condyle length and width (initial age: 2-3 weeks, observation period: 1-18 weeks). Condylar width (Enomoto et al., 2010) dimensions on micro-CT as well as condylar length on lateral x-rays were found to increase in hard diet animals. Regarding cartilage on histologic sections, one study (Enomoto et al., 2014) using 3 week old animals found a thicker hypertrophic zone in hard diet animals after feeding the different diets for 1 to 4 weeks.

4. Discussion

The present study aimed to systematically assess the evidence on the effect of food consistency (hard/soft diet) on four structural craniofacial components in healthy rodents, namely (1) the temporomandibular joint/condyle, (2) the condylar cartilage, (3) the molar alveolar bone and (4) the molar periodontal ligament. The use of experimental animals in research has led to societal debates due to ethical questions arising in conjunction to laboratory animal suffering for an expected/potential benefit to humans (de Vries et al., 2014). A weak design, conduct and analysis of scientific studies related to laboratory animals is likely to produce unreliable results and may lead to both research waste and animal waste (Ioannidis et al., 2014). An optimization of the above mentioned research procedures for future experimental animal studies may be reached through gathering of the available evidence and identifying knowledge gaps and current study limitations with the aid of systematic reviews and meta-analysis of previously performed experiments (de Vries et al., 2014; Hooijmans et al., 2014). Up to now, there is no known previous systematic review investigating the effect of dietary consistency on craniofacial components in rodents although there is a breadth of individual animal studies.

Rodents play a critical role in research, making up the largest part of all laboratory animals. The reasons for their choice may be considered rather clear: they are small, can easily be housed and maintained and do have a short lifespan (Gomes & Fernandes, 2011). An additional reason is their well-known genetic background that closely resembles those of human. Identifying the effect of food consistency on phenotypic variation in human populations is difficult. Genetic, developmental and environmental sources of variance interact, which in contrast can be better controlled when using laboratory animals for research purposes.

In the present meta-analysis, only a limited number of studies contributed to the polled estimated effect for condylar dimensions in both rats and mice. Overall, a significantly larger condylar process in terms of length and width was recorded for rats that received a hard diet as compared to those that were fed with soft diet. A similar conclusion was reached for mice. Experimental period typically allowed for a relatively short observation period of a month in growing animals.

Condylar cartilage (secondary cartilage) is a very heterogeneous tissue containing cells at various stages of chondrogenic maturation. The terminology and classification differed between the investigators, while it largely depends on animal species as well as growth stage of the tissue (Mizoguchi, Toriya, & Nakao, 2013). Most authors found an impact of either soft or hard diet on individual cartilage layers; however, meta-analysis was not possible due to large heterogeneity in the origin of the related measurements, and the localization and orientation of the sections used for histologic evaluation. Regarding molar alveolar bone of the mandible, an overall increased height and width was identified for the hard diet animals. Likewise, the heterogeneous investigation methods used for linear measurements were not compatible with data synthesis. Evidence assessing molar periodontal ligament was rather scarce to allow for a definite assessment.

The SYRCLE tool (Hooijmans et al., 2014) was used to assess the internal validity and evaluate the risk of bias within original studies. The overall quality of the considered studies was found to be low with related inherent unclear to high risk of bias. Selection bias was one of the main reporting shortcomings as no study reported details of randomization when assigning treatment alternatives. In addition to selection bias, detection bias cannot be overruled as it was unclear whether outcome raters of individual studies were blinded, irrespective of the nature of the outcome. This may reveal significant flaws in the design and reporting of animal studies which in turn may bear an effect on laboratory research waste. The SYRCLE risk of bias tool used in this systematic review was a first step towards transparency in the reporting of diet related rodent studies that will hopefully assist in improving design, conduct and analysis of future work.

The ARRIVE guidelines have been developed in 2010 (Kilkenny et al., 2010) in an attempt to improve reporting of animal research in general and have been used within the scopes of the present review in order to identify the reporting quality of the included articles. This approach has highlighted the need for improved and more standardised reporting as far as characteristics of animal populations involved in the experimental procedures are concerned. Although ARRIVE guidelines have been used in experimental research in other fields of dentistry (Berglundh & Stavropoulos, 2012), it seems that adherence to these standards remains suboptimal with regard to research in food dietary consistency and craniofacial structures.

In the present review, only studies with solid intervention schemes with the use of either soft or hard diet in isolation were considered. Studies with switching diet groups handled by cross- over type designs were excluded. The main reason for this was our intention to capture the net intervention effects on each of the four structures of the mandible, whilst confining the apparent carry- over effects of potential alternate interventions.

The main characteristic of the available evidence was the lack of consistency and the high level of heterogeneity in the methodologies followed in individual studies. This reflected not only differences in experimental settings but also lack of homogeneity in the age of animal populations, the duration of the experimental period as well as the outcome measures and means of evaluation considered. Apparently, there is an overriding need for standardization of procedures followed both at the stage of protocol development but also during the phase of outcome assessment. The development of core outcomes has been proposed in clinical research (Tsichlaki et al., 2017) and should be applicable in experimental research as well in an attempt to provide a live basis upon which the available evidence and gathered data would be synthesized and compared.

5. Conclusions

1. Overall, based on studies of unclear to high risk of bias, rats receiving a soft diet at an initial age of 3 to 4 weeks presented smaller condylar width and anteroposterior length dimensions after an experimental period of 4 to 5 weeks. In soft diet mice (initial age 2-3 weeks), a decreased condylar length was observed as well after 4 to 5 weeks experimental period.
2. Data synthesis with regard to condylar cartilage and alveolar bone was not possible due to heterogeneous measurement techniques and origins of analysis. In the case of periodontal ligament, evidence was very scarce.
3. A standardization of the experimental protocols and the intervention procedures is recommended, to prevent animal and research waste.

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Figure Captions

Figure 1. PRISMA flow diagram for the identification and selection of eligible studies.

Figure 2. Frequency distribution (%) of the scores assessed for each item of the ARRIVE guidelines in all studies included. Items were scored 0 (clearly inadequate), 1 (possibly inadequate) or 2 (clearly adequate)

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. The colors indicate low risk of bias (green), high risk of bias (red) or unclear risk of bias (yellow).

Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. The colors indicate low risk of bias (green), high risk of bias (red) or unclear risk of bias (yellow).

Figure 5. Random effects meta-analysis for the effect of soft versus hard diet on the anteroposterior condylar length in rats.

Figure 6. Random effects meta-analysis for the effect of soft versus hard diet on condylar width in rats.

Figure 7. Random effects meta-analysis for the effect of soft versus hard diet on the condylar length in mice.

Tables

Table 1. Checklist of the 20 items corresponding to the ARRIVE guidelines

	Items
1	Title
2	Abstract
3	Background
4	Objectives
5	Ethical statement
6	Study design
7	Experimental procedures
8	Experimental animals
9	Housing and husbandry
10	Sample size
11	Allocating animals to experimental groups
12	Experimental outcomes
13	Statistical methods
14	Baseline data
15	Numbers analyzed
16	Outcomes and estimation
17	Adverse events
18	Interpretation/scientific implications
19	Generalizability/translation
20	Funding

Table 2. Characteristics of included studies (rats)

Author	Population/age/number per group	Investigation method	Comparison	Outcome/observation time
(Orajarvi, 2015)	29 female rats (unclear strain) at the age of 60 days divided in a 7 days experimental group (8 HD vs 6 SD) and a 27 days experimental group (8 HD vs 7 SD)	Measurement of the total condylar cartilage thickness in the most central sagittal section (divided in ant., most sup. & post. segments) of histological sections	Hard versus soft diet animals	**CA:** No total cartilage thickness difference after 7 days in all 3 segments but reduced thickness in SD animals after 27 days in all 3 segments
Ikeda et al. (2014)	20 male Wistar rats at the age of 3 weeks (10 HD vs 10 SD)	Micro- CT analysis of mid- sagittal condylar specimens divided in ant., most sup. & post. regions.Measurement of the total condylar cartilage thickness in mid-sagittal direction (divided in ant., sup. & post. region) on histological sections	Hard versus soft diet animals	**TMJ/Co:** After 47 days the ratio bone volume/trabecular volume was lower in all 3 regions of SD animals, trabecular thickness was lower in sup. & post. region of SD animals while there was no difference between HD & SD animals in trabecular number, trabecular separation and trabecular spacing **CA:** Thicker total cartilage thickness and hypertrophic zone thickness in HD animals after 47 days in all 3 regions
(Hichijo et al., 2014)	14 male Wistar rats at the age of 3 weeks (7 HD vs 7 SD)	Measurement of the total condylar cartilage thickness in the intermediate region of mid-sagittal histological sections	Hard versus soft diet animals	**CA:** Thicker total cartilage thickness after 2 weeks in HD animals
(Guerreiro et al., 2013)	24 male Wistar rats (albinus norvegicus) at the age of 3 weeks (12 HD vs 12 SD)	Condyle length measurement on lateral photographs of dry mandibles (tangent line to the notches and then measured perpendicular to that line up to the highest portion of the condylar curve)	Hard versus soft diet animals	**TMJ/Co:** No difference in condylar length after 50 days between SD and HD animals
(Shimizu et al., 2013)	12 male Wistar rats at the age of 3 weeks (6 HD vs 6 SD)	Micro- CT analysis of the inter- radicular alveolar bone in the first molar region	Hard versus soft diet animals	**ABM:** Ratio bone volume/trabecular volume, trabecular thickness, trabecular number, trabecular spacing width & trabecular star volume was increased in HD animals after 9 weeks, whereas marrow space star volume was increased in SD animals
(Orajarvi et al., 2012)	16 female rats (unclear strain) at the age of 3 weeks (8 HD vs 8 SD)	Measurement of total condylar cartilage thickness in the most central sagittal section (divided in ant., most sup. & post. segments of equal lengths) of histological sections	Hard versus soft diet animals	**CA:** No difference in total cartilage thickness after 46 days in all 3 segments between HD and SD animals
(Orajarvi et al., 2011)	16 female rats (unclear strain) at the age of 3 weeks (8 HD vs 8 SD)	Measurement of proliferative cartilage layer thickness in the superior part of the most central sagittal section on histological sections	Hard versus soft diet animals	**CA:** Thicker proliferative layer in HD animals after 46 days
(Tiilikainen et al., 2011)	32 female Sprague Dawley rats at the age of 3 weeks (2x8 HD vs 2x8 SD)	Measurement of the total cartilage thickness in the most superior part of the most central sagittal section on histological sections	Hard versus soft diet animals	**CA:** Thicker total cartilage thickness after 33 days hard diet feeding compared to 30 days soft diet feeding. Same findings after 53 days hard diet feeding compared to 50 days soft diet feeding.

(Mavropoulos et al., 2010)	38 male Sprague Dawley rats at the age of 3 weeks (16 HD vs 22 SD)	Micro- CT analysis of the alveolar bone between and apical the first molar roots Height of the molar alveolar bone measured from the mandibular canal to the bifurcation of the first molar on micro- CT`s Width of the molar alveolar bone at the midlevel of the 1st molar apices on micro- CT`s	Hard versus soft diet animals	**ABM:** Ratio bone volume/trabecular volume, trabecular thickness, trabecular number and connectivity density was increased in HD animals, whereas trabecular separation and bone surface/bone volume was increased in SD animals after 27 weeks experimental period. Molar alveolar bone height was found to be increased in SD animals, while alveolar bone width was increased in HD animals after 27 weeks.
(Kingsmill et al., 2010)	14 female rats (unclear strain) at the age of 2 months (7 HD vs 7 SD)	Micro- CT analysis to determine the amount of bone volume in the furcation from the 1st to the 3rd molar. qSE-SEM to determine the mineral density on the buccal and lingual alveolar side.	Hard versus soft diet animals	**ABM:** Smaller amount of bone volume in SD animals after 20 experimental weeks (this difference disappeared after correction for weight). Soft diet lead to an increase in mineralization density on the lingual alveolar side while there was no difference on the buccal alveolar side after 20 weeks.
(Odman et al., 2008)	38 male Sprague Dawley rats at the age of 3 weeks (16 HD vs 22 SD)	Lateral photographs of transilluminated dry hemimandibles to measure molar alveolar anterior (first molar) and posterior height (third molar) as a perpendicular distance from the deepest point of the alveolar crest to a reference line through mandibular and mental foramina as well as condylar process area delimited by a tangent to both upper and lower mandibular notches. In evaluating condyle process length, a line was drawn tangent to the notches and then length was measured perpendicular to that lint to the highest portion of the condylar curve.	Hard versus soft diet animals	**ABM:** Anterior and posterior molar alveolar bone height was decreased in HD animals after 27 weeks. **TMJ/Co:** No difference between HD and SD condylar process area and condylar length after 27 weeks.
(Abed et al., 2007)	32 male Sprague Dawley rats at the age of 23 days (16 HD vs 16 SD)	Mandibular alveolar bone height was measured on lateral cephalograms as a distance from the junction of the alveolar bone and the mesial surface of the first mandibular molar perpendicular to a line through Gn (the most inferior point on the ramus) and I1 (the most anterior and superior point on the alveolar bone of the mandibular incisors)	Hard versus soft diet animals	**ABM:** Increased mandibular alveolar bone height in HD animals after 8 experimental weeks.
(Tanaka et al., 2007)	15 male Wistar rats at the age of 3 weeks (6 HD vs 9 SD)	Micro- CT analysis to determine the degree of mineralization in the center of the condyle and in the buccal cortical bone of the mandibular body	Hard versus soft diet animals	**TMJ/Co:** Degree of condylar trabecular bone mineralization higher in HD animals after 9 weeks. **ABM:** Degree of mineralization in the buccal bone was higher in SD animals after 9 weeks.
(Vaid et al., 2002)	30 (15 males and 15 females) “albino” rats at the age of 2 weeks (15	Maximum antero- posterior length and width measurement on dry condyle Maximum depth of the condylar cartilage on its lateral surface on dry condyle	Hard versus soft diet animals	**TMJ/Co:** Increased condyle length and width in HD animals after 8 weeks **CA:** Increased depth in HD animals after 8 weeks

	HD vs 15 SD, gender distribution unclear)			
(Maki et al., 2002)	20 male Wistar rats at the age of 3 weeks (10 HD vs 10 SD)	Micro- densiometry of the condyloid process area in reference to aluminium (mean bone mineral density of the whole region up to a line drawn tangent to the notches)	Hard versus soft diet animals	**TMJ/Co:** No difference in density between HD and SD animals after 6 weeks
(Kiliaridis et al., 1999)	20 male Sprague Dawley rats at the age of 4 weeks (10 HD vs 10 SD)	Anteroposterior length and width of the condyle was measured on axial photographs of dry mandibles Measurement of the hypertrophic zone cartilage thickness on projected most central sagittal sections in the anterior, intermediate and posterior part	Hard versus soft diet animals	**TMJ/Co:** Increased condylar length and width in HD animals after 4 experimental weeks **CA:** Decreased thickness in the anterior part of SD animals, no difference in the intermediate part and increased thickness in the posterior part of SD animals after 4 weeks
(Bresin et al., 1999)	28 male Sprague Dawley rats with an initial age of 90g (14 HD vs 14 SD). (This weight corresponds to 28 days of age after e- mail contacting with author)	Contact microradiographs of coronal condylar sections in antero- posterior direction in reference to aluminium as well as coronal sections perpendicular to the mandibular plane in the region between the medial and distal roots of the first molar	Hard versus soft diet animals	**TMJ/Co:** Bone mass 0,5- 1mm from the posterior edge of the condyle was increased in HD animals, while bone density in the lateral and medial cortical bone showed both no difference after 4 experimental weeks. **ABM:** Increased apical bone mass in HD animals, increased medial bone density in HD animals but no difference in the lateral cortical bone apical the first molar. Increased lateral thickness of the mandibular cortical bone in HD animals but no difference in the medial cortical bone after 4 weeks.
(Endo et al., 1998)	18 male Wistar rats with an initial age of 3 weeks were divided in 3 groups à 6 animals (3x3 HD vs 3x3 SD, group size not specified, no answer after contacting author)	Direct measurement of anteroposterior length and width on dry condyles Measurement of cartilage thickness at the center of the condyle in frontal direction	Hard versus soft diet animals	**TMJ/Co:** No difference in anteroposterior length was found between HD and SD animals after 10, 13 & 17 experimental weeks whereas width was increased in HD animal's at all three time points. **CA:** Thicker total cartilage thickness after 10, 13 and 17 experimental weeks in SD animals. Increased articular zone thickness, proliferative cell layer thickness, chondroblastic layer thickness and hypertrophic zone thickness in HD animals after 10, 13 and 17 experimental weeks.
(Kiliaridis et al., 1996)	28 male Sprague Dawley rats with an initial age of 4 weeks (14 HD vs 14 SD)	Standard x- ray of the mandibular half in reference to aluminium to determine bone mass	Hard versus soft diet animals	**TMJ/Co:** Bone mass in an area on the lateral half of the mandible situated 0.22mm anterior to the posterior border of the condyle was increased in HD animals after 4 experimental weeks. **ABM:** Bone mass in an area between and apical to the middle and distal roots of the first molar was increased in HD animals after 4 weeks.
(Bresin et al., 1994)	28 male "albino" rats with an initial age of 29 days (14 HD vs 14 SD)	Contact microradiograms of mandibular alveolar bone in coronal direction were cut perpendicular to the mandibular plane (starting from the 1st molar and reaching to the 3rd molar).	Hard versus soft diet animals	**PL:** Buccal periodontal space width was increased in HD animals but there was no difference in lingual periodontal space width after 4 experimental weeks. **ABM:** Measurement from the most buccal point to the most lingual point showed increased width in HD animals after 4 weeks

(Yamada & Kimmel, 1991)	24 female rats (unclear strain) with an initial age of 3 weeks were divided in 2 groups à 12 animals (2x6 HD vs 2x6 SD)	Parasagittal histological sections of the condyle to determine trabecular bone volume of the primary and secondary spongiosa as well as superior condylar cartilage thickness	Hard versus soft diet animals	**TMJ/Co:** The trabecular bone volume of the primary and secondary spongiosa was increased in HD animals after 4 weeks but there was no difference after 8 weeks. **CA:** The proliferative cell layer thickness of the superior condylar cartilage showed no difference after 4 weeks but was thicker in the HD animals after 8 weeks, whereas the thickness of the chondroblastic layer showed no difference at both time points. The hypertrophic zone was thicker after 4 weeks in HD animals and showed no difference after 8 weeks.
(Bouvier, 1988)	54 Sprague Dawley rats with an initial age of 3 weeks (9f & 7m HD vs 9f & 7m SD = growing rats) and approximately 4 months (12m HD & 10m SD = mature rats)	Histological central portion sections of the condyle in coronal direction to evaluate subcondylar trabecular bone area Direct length and width measurement on the dry condyle Measurement of cartilage thickness at the central portion of the condyle in coronal direction	Hard versus soft diet animals	**TMJ/Co:** Subcondylar trabecular bone area of growing (after 4 weeks) and mature rats (after 12 weeks) increased in HD animals. Anteroposterior length and width (separated according to sex) of growing females, growing males and mature males were increased in HD animals compared to SD animals. **CA:** Total cartilage thickness, articular zone thickness, proliferative zone thickness, chondroblastic zone thickness and hypertrophic zone thickness of growing (after 4 weeks) and mature rats (after 12 weeks) (sex for this measurement not separated) was thicker in HD animals
(Bouvier & Zimny, 1987)	53 Sprague Dawley rats with an initial age of 4 weeks (9f & 6m HD vs 9f & 3m SD = growing rats) and “mature” animals (14m HD & 12m SD = mature rats)	Direct length and width measurement on dry condyle	Hard versus soft diet animals	**TMJ/Co:** Anteroposterior length and width (separated according to sex) of growing females, growing males (both after 4 weeks) and mature males (after 12 weeks) were increased in HD animals.
(McFadden et al., 1986)	19 Fischer strain albino rats with an initial age of 3 weeks (5f & 4m HD vs 5f & 5m SD)	A line was drawn tangent to the notches (on lateral photograph of dry mandible). Length was measured perpendicular to that line up to the highest portion of the condylar curve	Hard versus soft diet animals	**TMJ/Co:** HD animals showed increased length (but they found a sexual dimorphism: smaller values in females) **:** After 16 experimental weeks
(Hinton & Carlson, 1986)	15 male Sprague Dawley rats with an initial age of 3 weeks (7 HD vs 8 SD)	Histological sections of the condyle in sagittal direction	Hard versus soft diet animals	**TMJ/Co:** Visual evaluation showed a reduced density and size of the trabeculation in SD animals after 26 days **CA:** Total cartilage thickness, proliferative cell layer thickness and chondroblastic layer thickness was reduced in SD animals in the superior region after 26 days. No difference in the posterior and posterosuperior region.
(Bouvier & Hylander, 1984)	20 male Long Evans rats with an initial age of 23 days (5 HD vs 5 SD = weanling rats) and 6 weeks (5 HD vs 5 SD = juvenile rats)	Histological sections of the condyle in sagittal direction (one SD condyle was damaged, unclear if weanling or juvenile) Direct length and width measurement on dry condyle Maximum depth of the condylar cartilage on its lateral surface of dry condyle	Hard versus soft diet animals	**TMJ/Co:** Visual evaluation showed a reduced quantity of the subchondral bone in both weanling (after 5 weeks) and juvenile SD rats (after 8 weeks). Both HD weanling and juvenile rats showed increased width and length dimensions of the condyle. **CA:** In the superior region of the condyle at its thickest portion the total cartilage thickness, articular zone thickness and proliferative cell layer thickness was increased in weanling HD animals but showed no difference in juvenile animals. The

				hypertrophic zone thickness showed no difference in both weanling and juvenile animals. Increased condylar depth in weanling and juvenile HD animals
(Beecher & Corruccini, 1981a)	30 male and 30 female Sprague Dawley rats (unclear distribution) with an initial age of 3 weeks (30 HD vs 30 SD)	Direct anteroposterior length measurement on dry condyle	Hard versus soft diet animals	**TMJ/Co: N**o difference between HD and SD animals was found after 4 months
(Stahl & Dreizen, 1964)	26 male Sprague Dawley rats with an initial age of 5 weeks (13 HD vs 13 SD)	Central mesio-distally oriented sections of the mandibular first and second molars.	Hard versus soft diet animals	**PL:** SD animals showed a narrower periodontal membrane after 68,49 weeks in comparison to HD animals after 70,86 weeks
(Barber et al., 1963)	30 male Long Evans rats with an initial age of 3 weeks (15 HD vs 15 SD)	On a projected silhouette of the condyle a line was drawn tangent to the deepest depression on each side of the condyle. Length was measured perpendicular to that line to the highest portion of the condylar curve. Area between the point of deepest depression between the condyloid process and the point of deepest depression between the condyloid process and the angular process was measured on a projected silhouette of the condylar process	Hard versus soft diet animals	**TMJ/Co:** No difference in condylar length between HD and SD animals after 18 experimental weeks Increased condylar process area in HD animals compared to SD animals after 18 weeks
(Watt & Williams, 1951)	60 rats (unclear strain) with an initial age of "approx." 3 weeks (16m & 14f HD vs 16m & 14f SD)	Standard radiograph of hemimandible using a constant technique. Measurement of molar alveolar bone width on dry mandibles in the region of the distal root of the 1st molar.	Hard versus soft diet animals	**TMJ/Co:** Visual evaluation showed denser articulating condylar surfaces in HD animals after 4 months **ABM:** Thicker molar alveolar bone width in HD animals after 4 months

f, female; m, male; HD, hard diet; SD, soft diet; TMJ/Co, temporomandibular joint/condyle; ABM, mandibular alveolar bone; CA, condylar cartilage; PL, periodontal ligament.

Table 3. Characteristics of included studies (mice).

Author	Population/age/number per group	Investigation method	Comparison	Outcome/observation time
(Enomoto et al., 2014)	20 male CD-1 mice at the age of 3 weeks divided in a 1 week experimental group (5 HD vs 5 SD) and a 4 week experimental group (5 HD vs 5 SD)	Measurement of the total condylar cartilage thickness, the APC- zone (articular, proliferative and chondroblastic zone) and the hypertrophic zone in the most central coronal section of histological sections	Hard versus soft diet animals	**CA:** No total cartilage and APC- zone thickness differences after 1 respectively 4 weeks in the superior region. In contrast thickness of the hypertrophic zone was increased after both 1 and 4 weeks in HD animals.
(Enomoto et al., 2010)	20 male imprinting control region mice at the age of 3 weeks (10 HD vs 10 SD)	Condylar width (left-to-right thickness of the condyle) and condylar length (in the lateral view) was measured on micro- CT`s	Hard versus soft diet animals	**TMJ/Co:** Condyle width increased after 1 experimental week in HD animals but no difference after 4 experimental weeks. No difference in condylar length after both 1 and 4 experimental weeks
(Ito et al., 1988)	100 HD and 100 SD male C3H/He mice at the age of 2 weeks were divided in 1, 3, 5, 10 and 18 weeks experimental subgroups	Measurement of the condyle process length with soft x- ray arrangement (lateral view)	Hard versus soft diet animals	**TMJ/Co:** Increased condyle length in HD animals after 1, 3, 5, 10 and 18 experimental weeks

HD, hard diet; SD, soft diet; TMJ/Co, temporomandibular joint/condyle; CA, condylar cartilage.

Appendix 1

MEDLINE search

Limits: no language restriction applied

Publication date: no restriction

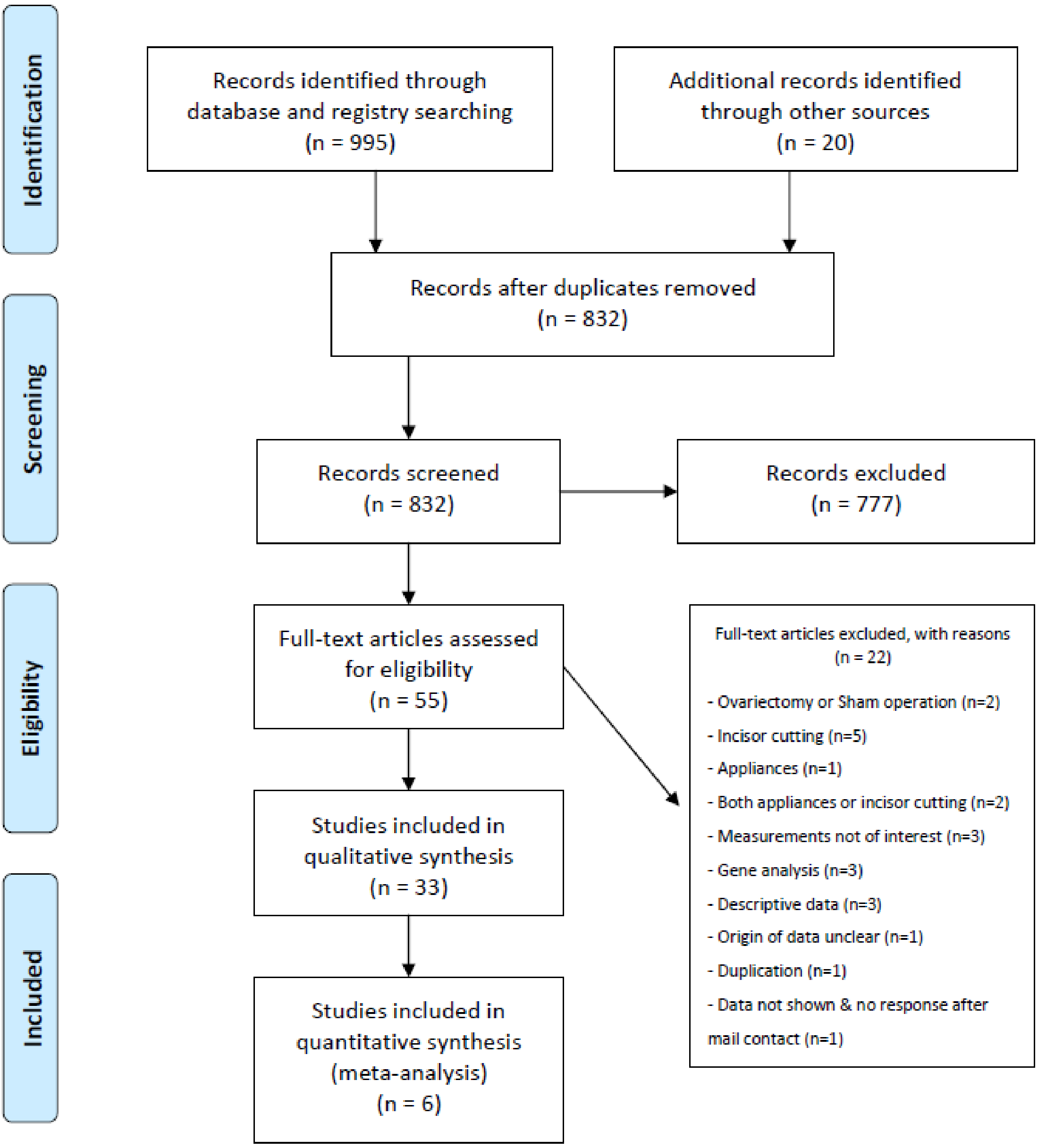
Search Builder: ‘All Fields’

Four consecutive searches combined with "AND" Boolean operator, using “OR” between free text terms or keywords:

1. mice
2. mouse
3. rat
4. rat*
5. rodent
6. 1 OR 2 OR 3 OR 4 OR 5
7. alveolar bone
8. mandible
9. mandib*
10. alveol*
11. condyle
12. condyl*
13. condylar bone
14. periodontal ligament
15. periodontal ligament space
16. bone density
17. cartilage
18. mandibular cartilage
19. condylar cartilage
20. temporomandibular joint
21. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20

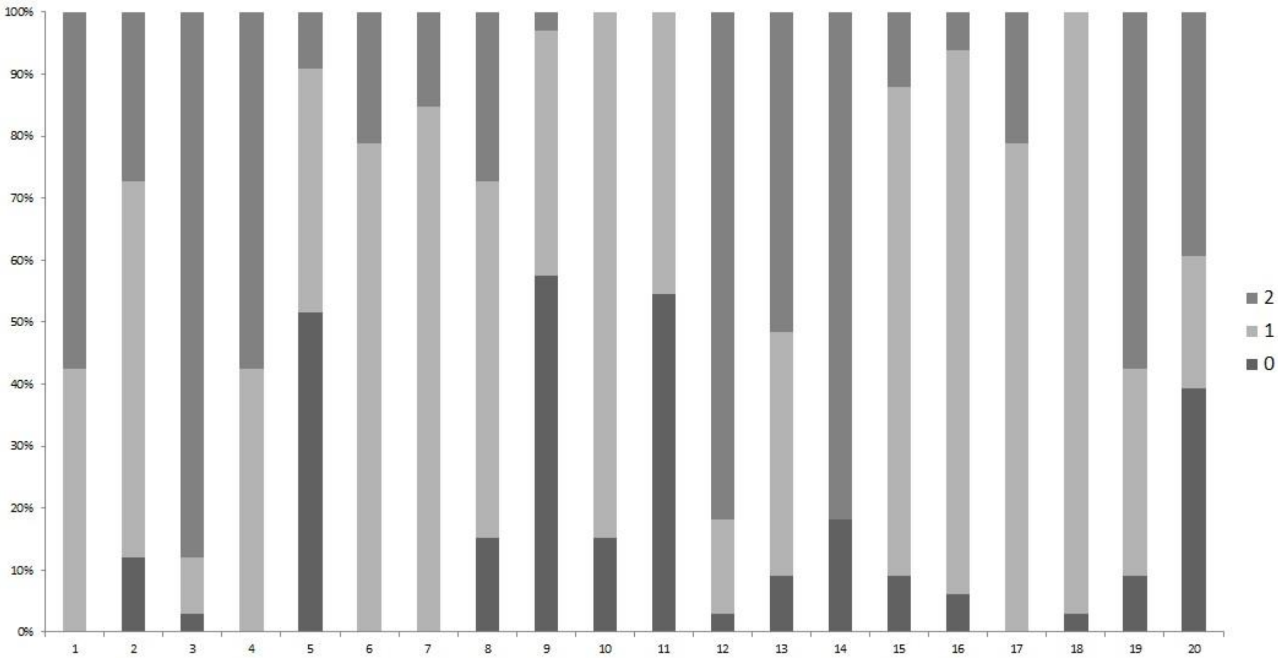
22. hard diet
23. soft diet
24. Masticatory function
25. 22 OR 23 OR 24
26. 6 AND 21 AND 25

Figure 1



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 2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10%
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20
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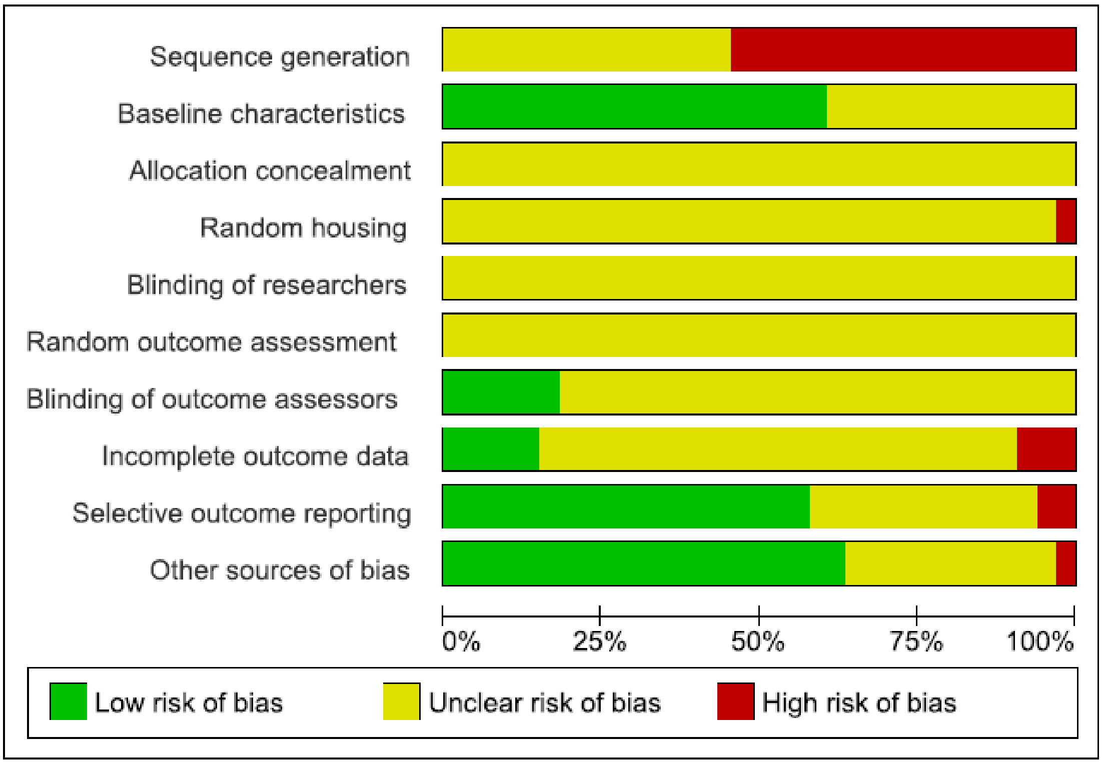
0

Figure 3



Sequence generation
Baseline characteristics
Allocation concealment
Random housing
Blinding of researchers
Random outcome assessment
Blinding of outcome assessors
Incomplete outcome data
Selective outcome reporting
Other sources of bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Figure 4

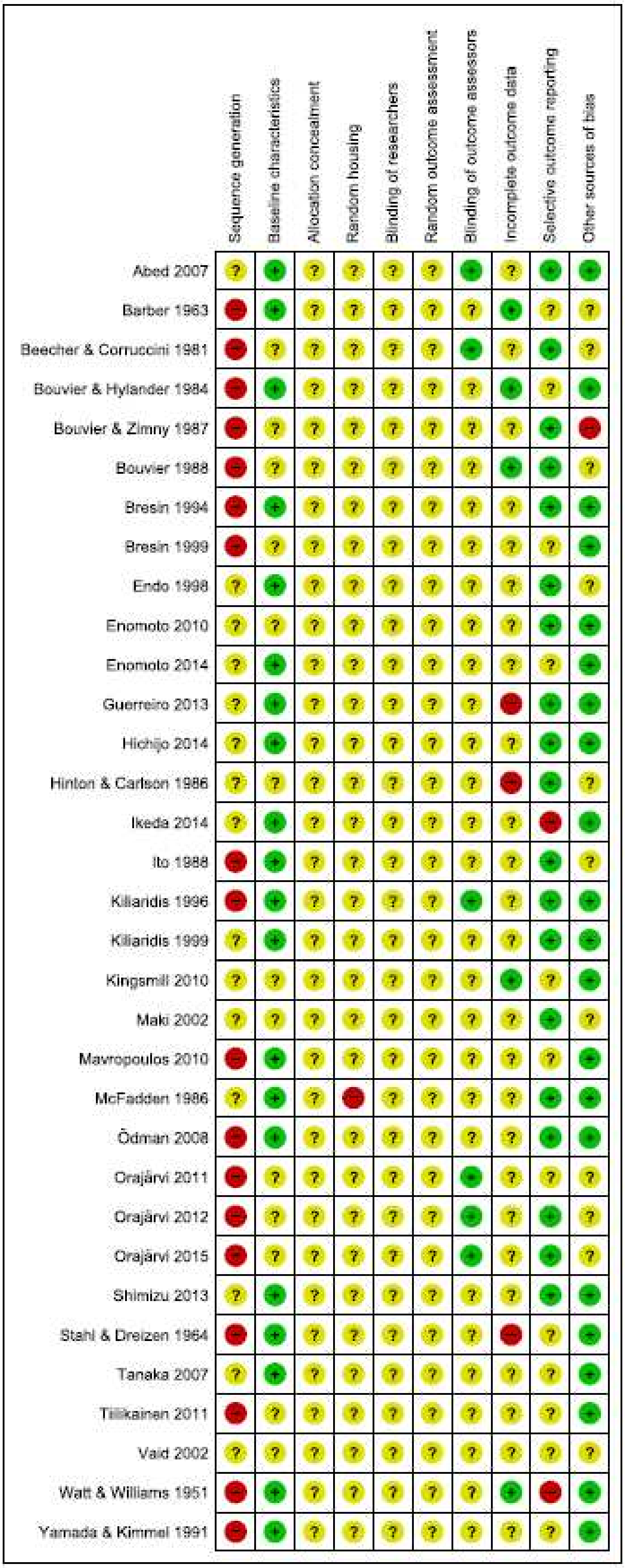

Sequence generation
Baseline characteristics
Allocation concealment
Random housing
Blinding of researchers
Random outcome assessment
Blinding of outcome assessors
Incomplete outcome data
Selective outcome reporting
Other sources of bias
Abed 2007
Barber 1963
Beecher & Corruccini 1981
Bouvier & Hylander 1984
Bouvier & Zimny 1987
Bouvier 1988
Bresin 1994
Bresin 1999
Endo 1998
Enomoto 2010
Enomoto 2014
Guerreiro 2013
Hichijo 2014
Hinton & Carlson 1986
Ikeda 2014
Ito 1988
Kiliaridis 1996
Kiliaridis 1999
Kingsmill 2010
Maki 2002
Mavropoulos 2010
McFadden 1986
Ödman 2008
Orajärvi 2011
Orajärvi 2012
Orajärvi 2015
Shimizu 2013
Stahl & Dreizen 1964
Tanaka 2007
Tiilikainen 2011
Vaid 2002
Watt & Williams 1951
Yamada & Kimmel 1991

Figure 5

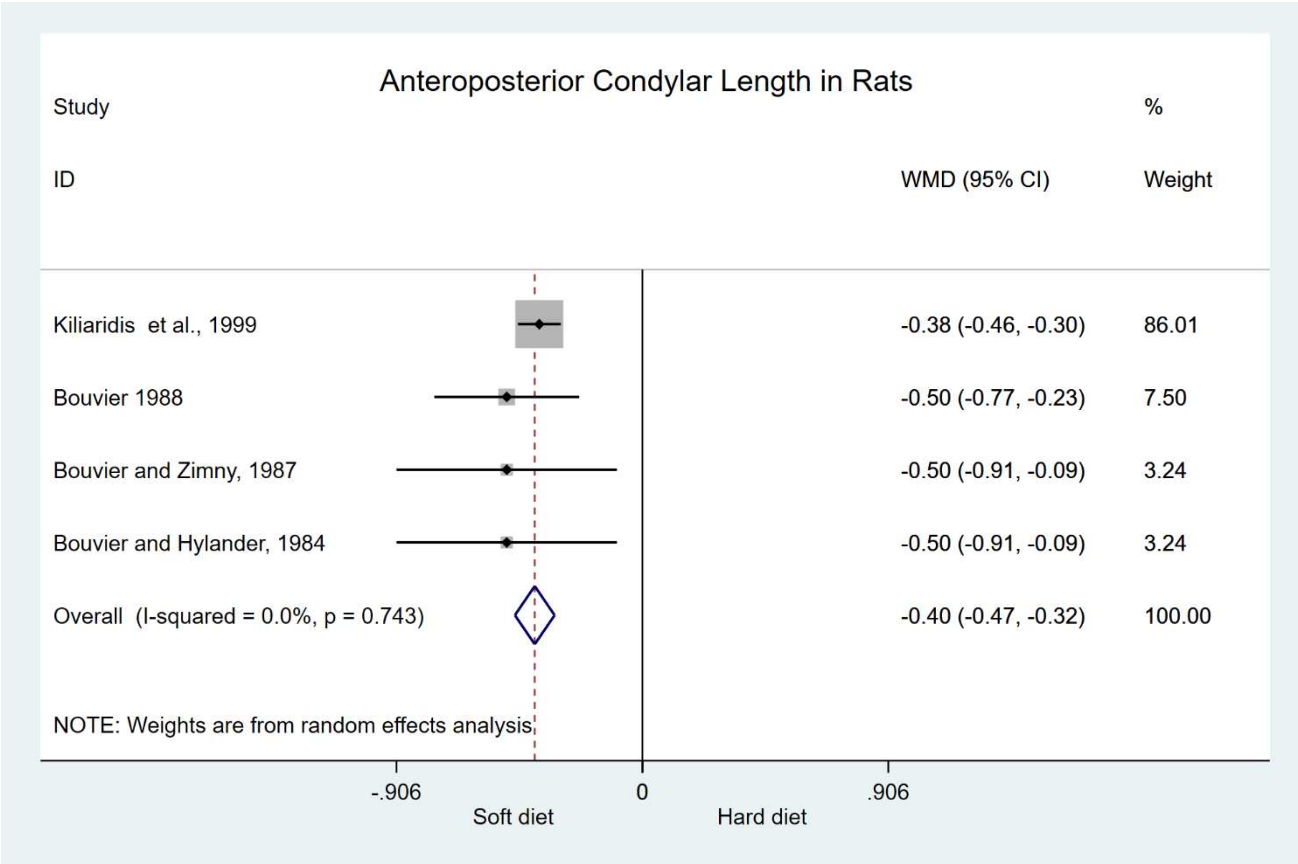

Anteroposterior Condylar Length in Rats
Study
ID
%
WMD (95% CI)
Weight
Kiliaridis et al., 1999
-0.38 (-0.46, -0.30)
86.01
Bouvier 1988
-0.50 (-0.77, -0.23)
7.50
Bouvier and Zimny, 1987
-0.50 (-0.91, -0.09)
3.24
Bouvier and Hylander, 1984
-0.50 (-0.91, -0.09)
3.24
Overall (I-squared = 0.0%, p = 0.743)
-0.40 (-0.47, -0.32)
100.00
NOTE: Weights are from random effects analysis
-.906
0
.906
Soft diet
Hard diet

Figure 6

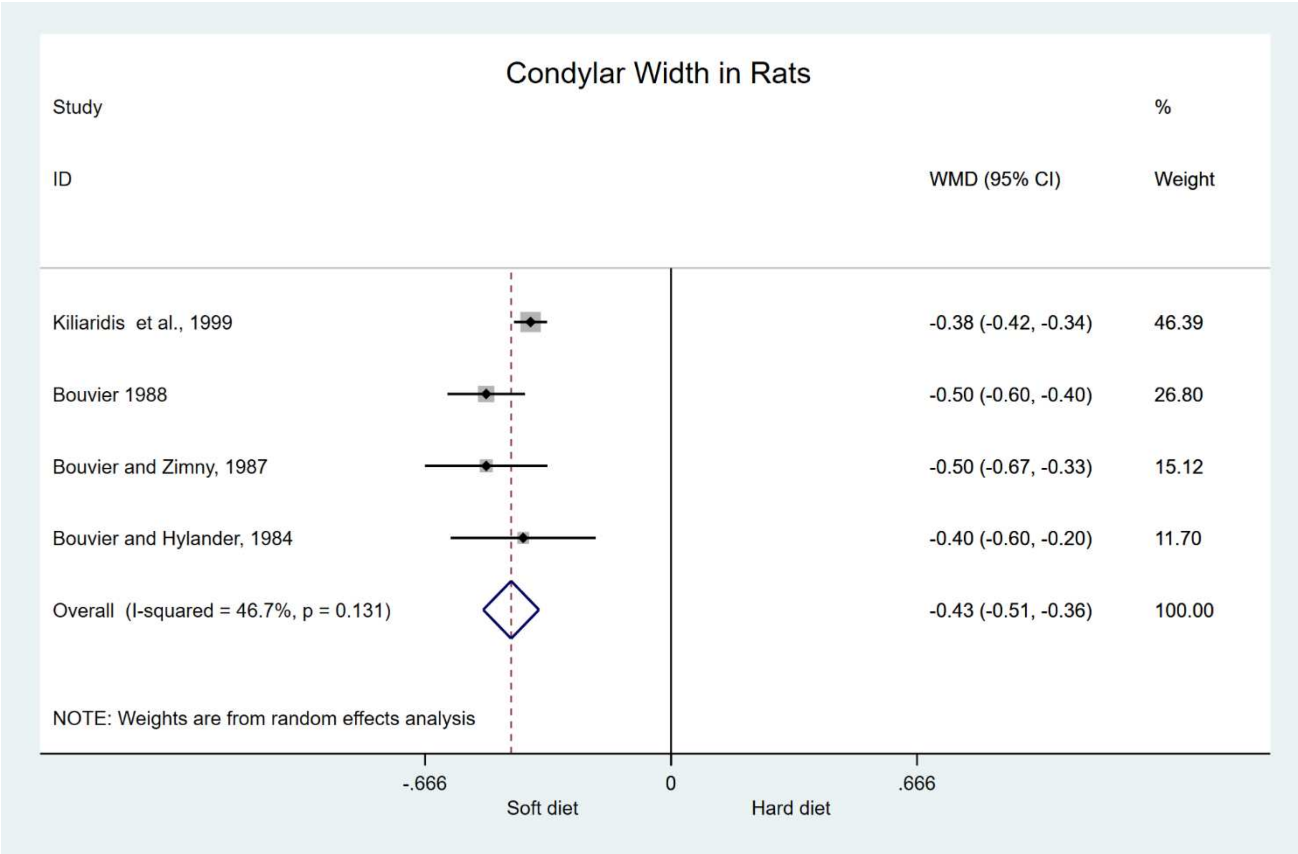
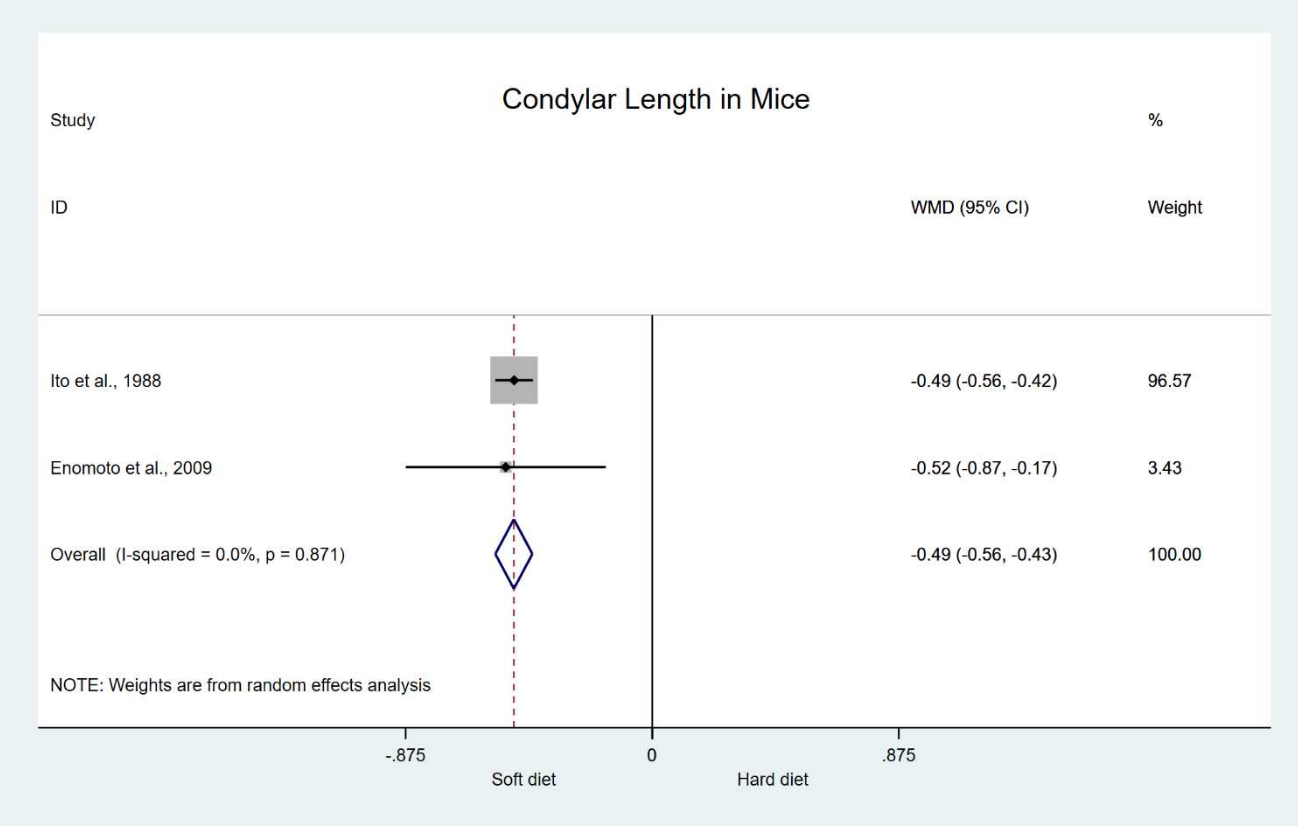

Condylar Width in Rats
Study
ID
WMD (95% CI)
%
Weight
Kiliaridis et al., 1999
-0.38 (-0.42, -0.34)
46.39
Bouvier 1988
-0.50 (-0.60, -0.40)
26.80
Bouvier and Zimny, 1987
-0.50 (-0.67, -0.33)
15.12
Bouvier and Hylander, 1984
-0.40 (-0.60, -0.20)
11.70
Overall (I-squared = 46.7%, p = 0.131)
-0.43 (-0.51, -0.36)
100.00
NOTE: Weights are from random effects analysis
-.666
0
.666
Soft diet
Hard diet

Figure 7


Condylar Length in Mice
Study ID
WMD (95% CI)
% Weight
Ito et al., 1988
-0.49 (-0.56, -0.42)
96.57
Enomoto et al., 2009
-0.52 (-0.87, -0.17)
3.43
Overall (I-squared = 0.0%, p = 0.871)
-0.49 (-0.56, -0.43)
100.00
NOTE: Weights are from random effects analysis
-.875
0
.875
Soft diet
Hard diet